

VITAMIN C LEVELS IN PREGNANT WOMEN AND EFFICACY OF VITAMIN C SUPPLEMENTS IN THE PREVENTION OF PRETERM BIRTH: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

We aimed to conduct a systematic review and meta-analysis to investigate if there is a significant difference in vitamin C blood levels in women who had preterm birth compared to control group who did not and evaluate the efficacy of vitamin C supplements in preventing it. This manuscript presents a part of a larger systematic review and meta-analysis which was registered in PROSPERO (CRD42022371644). PubMed/MEDLINE, Scopus and Web of Science were searched up to February 15, 2024. Forward and backward citation searching was also performed. Studies were selected according to prespecified inclusion and exclusion criteria. Data were analyzed using Meta-Essentials: Workbooks for meta-analysis (Version 1.5). A total of 10 studies (11 reports) met all eligibility criteria: 5 studies (5 reports) assessing vitamin C levels and 5 studies (6 reports) assessing efficacy. No significant difference was found in vitamin C levels between women who had preterm birth and controls who had term delivery (Hedges' $g=0.33$; 95% confidence interval [CI]: $-0.22, 0.88$; $p=0.091$; $I^2=53.50\%$). Also, no differences were seen between women supplemented with vitamin C and controls taking placebo or having no vitamin C supplementation in the risk of preterm birth (risk ratio=0.94; 95% CI: 0.57, 1.55; $p=0.730$; $I^2=50.13\%$). Significant level of heterogeneity was observed in both meta-analyses, but results were robust in all sensitivity analyses. Our results suggest that there are no significant differences in vitamin C levels between women with preterm and term birth and that vitamin C supplementation doesn't influence the risk of preterm birth.

Keywords: Vitamin C, preterm birth, systematic review, meta-analysis.

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INTRODUCTION

Preterm birth is defined as birth after 20 and before 37 completed weeks of gestation (1). Preterm birth rates were estimated to range from 4 to 18% depending on the country, with a global rate of about 11%, but these figures seem to be rising in recent years (2). Approximately 50% of preterm births have an unknown cause, about 25% are associated with premature (prelabor) rupture of membranes (PROM), and the remaining 25% are attributed to medically indicated or elective preterm deliveries (3,4).

Vitamin C, or ascorbic acid, is an essential water-soluble vitamin which has a role in the synthesis of collagen and acts as an antioxidant (5,6). However, the role of antioxidants, including vitamin C, in preterm and term birth is not entirely clear (7). Some studies reported that pregnant women who had preterm birth had significantly higher vitamin C level in their blood compared to those who gave birth at term (7,8), while others found no significant difference (9–11). To the best of our knowledge, up to now there are no systematic review and meta-analysis evaluating vitamin C blood levels in women who had preterm birth compared to those who did not. However, there are some older systematic reviews and meta-analyses which evaluated the effects of vitamin C supplementation in the prevention of preterm birth, but with conflicting results. First, published in 2005, concluded that women supplemented with vitamin C were at increased risk of giving birth preterm compared to placebo (12). In 2015, the updated systematic review and meta-analysis reported no clear differences between women supplemented with vitamin C compared with placebo or no control for the risk of preterm birth (6). Also, a systematic review and meta-analysis conducted in 2017 and published as a congress abstract in 2018 reported that vitamin C was not associated with a reduction in risk of preterm birth (13).

Considering previous conflicting evidence, we aimed to conduct a systematic review and meta-analysis to investigate if there is a significant difference in vitamin C blood levels in women who had preterm birth compared to control group who did not and evaluate the efficacy of vitamin C supplements in preventing it.

METHODS

This systematic review and meta-analysis presents a part of a larger systematic review and meta-analysis registered in the International Prospective Register of Systematic Reviews PROSPERO (registration number: CRD42022371644). Current manuscript reports results regarding preterm birth, while results regarding PROM were reported elsewhere as well as the complete search strategy (14). Briefly, three electronic databases (PubMed/MEDLINE, Scopus, Web of Science) were searched independently by two authors from the beginning of indexing up to December 21, 2022, without any language or date restriction. The search was last updated on February 15, 2024. Both backward and forward citation searching on publications that met the eligibility criteria were

conducted. Backward citation searching was conducted by inspecting the lists of references in these studies, while forward citation searching was conducted by using the Google Scholar citation index to identify citing studies on February 15, 2024. We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement (15).

Eligibility criteria and selection process

For the part regarding vitamin C level, the inclusion criteria were an original clinical study of any type which reported maternal peripheral blood, serum or plasma vitamin C level measured at any point during pregnancy or at/after delivery with a study group consisting of pregnant women who experienced preterm birth and a control group of pregnant women whose pregnancy ended in term delivery.

For the part regarding vitamin C supplementation efficacy, the inclusion criteria were randomized controlled clinical studies evaluating the efficacy of vitamin C supplementation alone in preventing preterm birth in pregnant women in comparison with a control group who received no vitamin C supplementation or placebo.

We excluded studies with unavailable full text, conference abstracts, and studies for which we could not extract, calculate, or obtain information needed for calculation of combined effect sizes. Specific exclusion criteria for the part regarding vitamin C supplementation efficacy were non-randomized clinical studies and studies in which the efficacy of vitamin C in combination with other supplements was evaluated (study was not excluded if both groups received the same supplements).

Two authors independently evaluated the eligibility of retrieved publications based on their title and abstract. When these were insufficient for evaluation, we sought to retrieve and evaluate the full text. Also, we tried to contact the authors of a total of three reports (16–18) with a request for clarifications or providing information about relevant data that were not available in the retrieved full texts. Publications were included in the meta-analysis if all authors agreed that the eligibility criteria were met. Disagreements between individual judgements were resolved by the first author.

Data extraction

The data extraction sheet was created, and two authors independently extracted data from the included studies. We extracted the following for all studies: study ID, citation, country/region, characteristics of the sample (e.g., participant groups and their main characteristics, sample sizes, age), and relevant findings/conclusions of the study. Furthermore, we extracted the following for studies measuring vitamin C levels: mean and standard deviation (SD) of the vitamin C level, measurement method, blood sample type, time of taking the blood sample, gestational age, and percentage of smokers in each group. Also, we extracted the following for studies evaluating vitamin C supplementation efficacy: inclusion criteria

in relation to gestational age and previous history of preterm birth, information about vitamin C supplementation (e.g., timing of commencement/duration of supplementation, dosage), type of control (no vitamin C supplementation, placebo), information about blinding, frequency of preterm birth in each group, and reported information about observed side effects associated with vitamin C supplementation. The first author double-checked the accuracy of the extracted data and created the final data extraction table by collating the two tables. The final data extraction table is publicly available in the Figshare repository (19).

Methodological quality (risk of bias) assessment

The methodological index for non-randomized studies (MINORS) tool (20) was used to assess the methodological quality (risk of bias) of the included studies of vitamin C level measurements. The MINORS tool has a total of 12 methodological items (20). Each item is scored from 0 to 2: 0 (not reported), 1 (reported but inadequate) and 2 (reported and adequate) (20). The global ideal score for comparative studies is 24 (20). Quality assessment of individual studies according to total MINORS score was categorized as follows: very low (0–6), low (7–12), moderate (13–18), and high (19–24) quality (21).

Cochrane Risk of Bias 2 (RoB 2) tool (22) was used to assess risk of bias of included randomized studies assessing the efficacy of vitamin C supplementation and Robvis web app was used for visualizing assessment (23).

All authors individually assessed the risk of bias of each study, while differences in assessment were resolved by discussion until a consensus was reached.

Data analysis

Meta-Essentials: Workbooks for meta-analysis (Version 1.5) (24) was used to analyze the data.

For the part regarding vitamin C levels, we used the random effects model and estimated the combined effect sizes by using Hedges' g with its 95% confidence interval (CI), prediction interval (PI) and corresponding tests of significance. We used means and SDs of vitamin C levels and a corresponding number of participants in the analyses. Standard errors were converted to SDs using the number of patients when needed.

For the part regarding the efficacy of vitamin C supplementation, we used a random effects model with an inverse variance weighting method while the combined effect sizes were estimated using risk ratio (RR) with its 95% CI, PI and corresponding tests of significance. Numbers of participants with outcome of interest (preterm birth) and corresponding denominators (number randomized minus any participants whose outcomes were known to be missing) were used in the analyses. The random effects model was used in all analyses because of the clinical and methodological heterogeneity of included studies, while the combined effect sizes were

considered significant if the associated 95% CI did not include zero (for Hedges' g) or one (for RR) and the associated two-tailed p -value was less than 0.05.

Cochran's Q test and I^2 statistic were used to evaluate statistical heterogeneity. Because Cochran's Q test can have low power when studies have a small sample size or are few in number, a p -value of <0.10 was considered to indicate the presence of statistically significant heterogeneity (25). An I^2 value $>50\%$ was considered significant. To explore sources of significant heterogeneity, additional subgroup analyses were performed in relation to available data (for levels in relation to measurement method, region [continent], blood sample type, and MINORS quality category; for efficacy in relation to overall risk of bias and region [continent]), along with moderator analysis with available continuous moderator variables (mean age for levels; total daily vitamin C dose for efficacy).

We carried out sensitivity analysis by removing one study at a time and recalculating the estimates of combined effect size for the remaining studies.

To assess the certainty of evidence for the efficacy outcome we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for summarizing confidence in effects of interventions (26).

RESULTS

The PRISMA flow diagram describing the results of the search and selection process is provided in Figure 1. Only one author of one study published in two reports (16,17) provided the requested data and clarifications. A total of 10 studies (11 reports) met all eligibility criteria: 5 studies (5 reports) assessing vitamin C levels (7–11) and 5 studies (6 reports) assessing efficacy (16,17,27–30).

Main characteristics of included studies are summarized in Table 1 and Table 2. Some side effects associated with vitamin C supplementation were reported only in one study where one woman reported stomach pain after taking a vitamin C tablet (16,17). There were no side effects of vitamin C supplementation in two studies (27,28).

Quality (risk of bias) assessment for each study is shown in Table 1 (for studies assessing levels) and Figure 2 (for efficacy studies). The MINORS quality score ranged from 14 to 18 of 24, so all five studies assessing vitamin C levels had moderate quality. The overall risk of bias for efficacy studies according to the RoB 2 tool was judged as "high" and "some concerns" for two (40.0%) and three (60.0%) of five studies, respectively.

There was no significant difference in vitamin C levels between women who had preterm birth and controls (five studies, 297 participants; Hedges' $g=0.33$; 95% CI: $-0.22, 0.88$; PI: $-0.69, 1.35$; $Z=1.69$, $p=0.091$; forest plot shown in Figure 3), but between-study heterogeneity was significant ($Q=8.60$, $p=0.072$, $I^2=53.50\%$). A subgroup of studies

conducted in Asia in which levels were measured using spectrophotometry (7,11) was without any heterogeneity ($I^2=0.00\%$), while the combined effect size was significant (Hedges' g 0.51 with 95% CI from 0.41 to 0.61) and indicated that vitamin C levels were significantly higher in women who experienced preterm birth. Sensitivity analysis did not show significant changes with the exclusion of individual studies.

In addition, no differences were seen between women supplemented with vitamin C and controls in the risk of preterm birth (five studies, 1643 participants; $RR=0.94$; 95% CI: 0.57, 1.55; PI : 0.38, 2.35; $Z=-0.34$, $p=0.730$; forest plot shown in Figure 3) and these results were robust in sensitivity analysis, but there was a significant between-study heterogeneity ($Q=8.02$, $p=0.091$, $I^2=50.13\%$). Subgroups of studies conducted in Africa (28–30) and continents other than Africa

(16,17,27) had acceptable level of heterogeneity ($I^2=43.86\%$ and $I^2=0.00\%$, respectively) and combined effect sizes were not significant ($RR=1.10$ with 95% CI from 0.56 to 2.18 and $RR=0.52$ with 95% CI from 0.17 to 1.59, respectively). Also, a subgroup of studies with high risk of bias (16,17,28) was without any heterogeneity ($I^2=0.00\%$) and with a nonsignificant combined effect size ($RR=0.77$ with 95% CI from 0.03 to 22.90). Certainty of the evidence assessment using the GRADE approach for the efficacy outcome was rated as low indicating that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. We downgraded for two levels: one level for serious risk of bias (overall risk of bias in all included studies was rated as either “some concerns” or “high”) and one level for serious imprecision (wide confidence intervals).

Figure 1. Results of the search and selection process (PRISMA flow diagram)

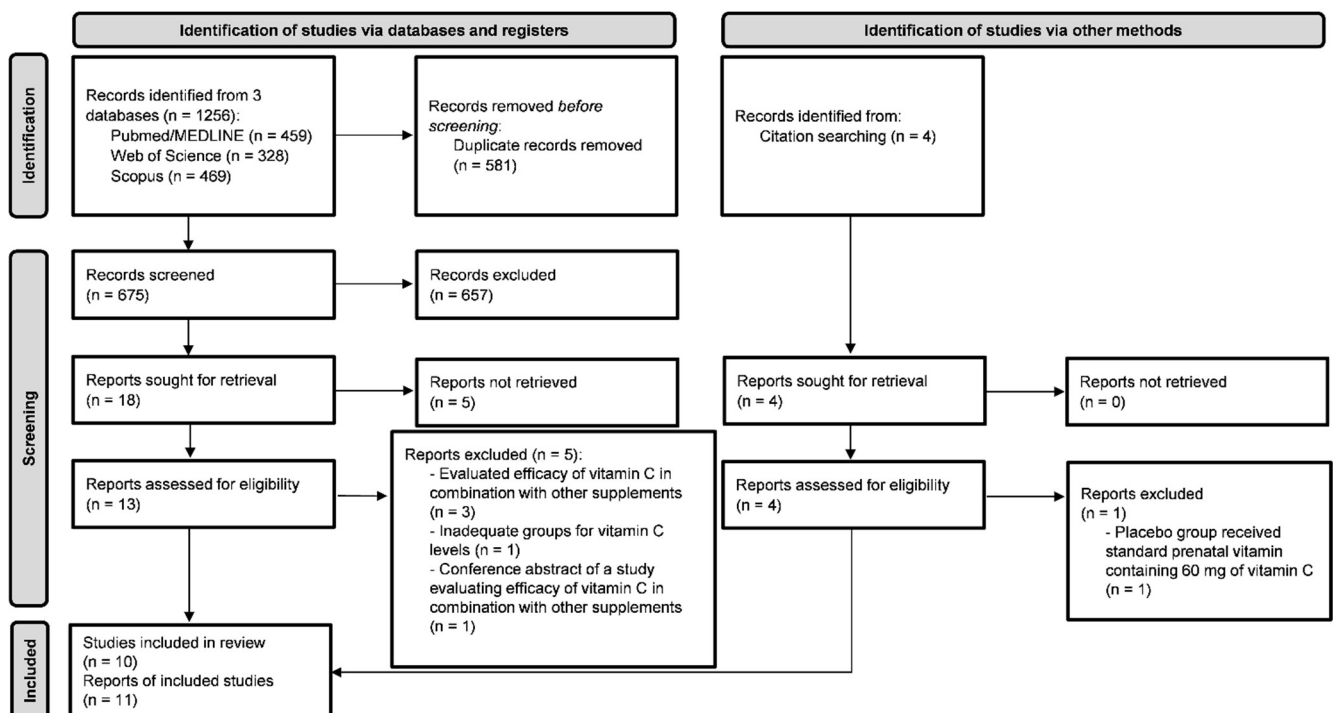
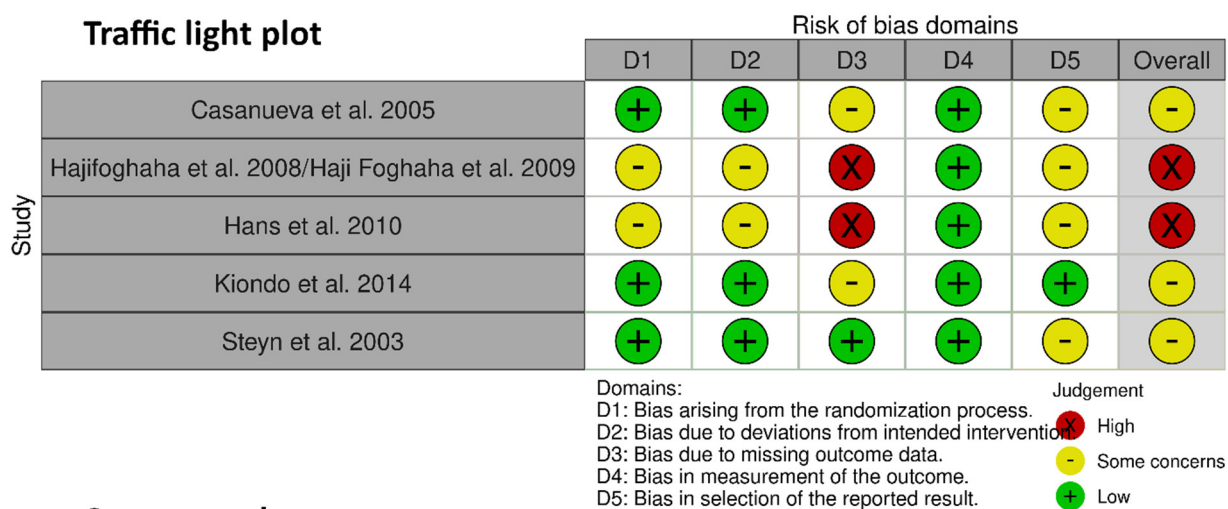


Figure 2. Risk of bias assessment of efficacy studies according to the RoB 2 tool

Summary plot

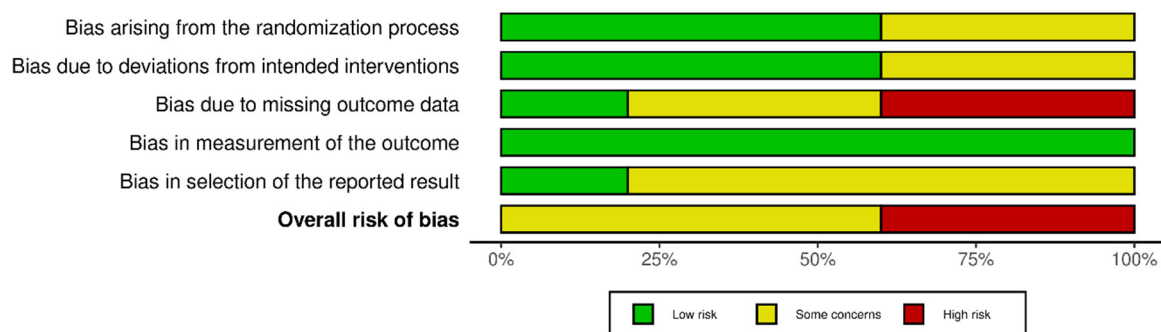
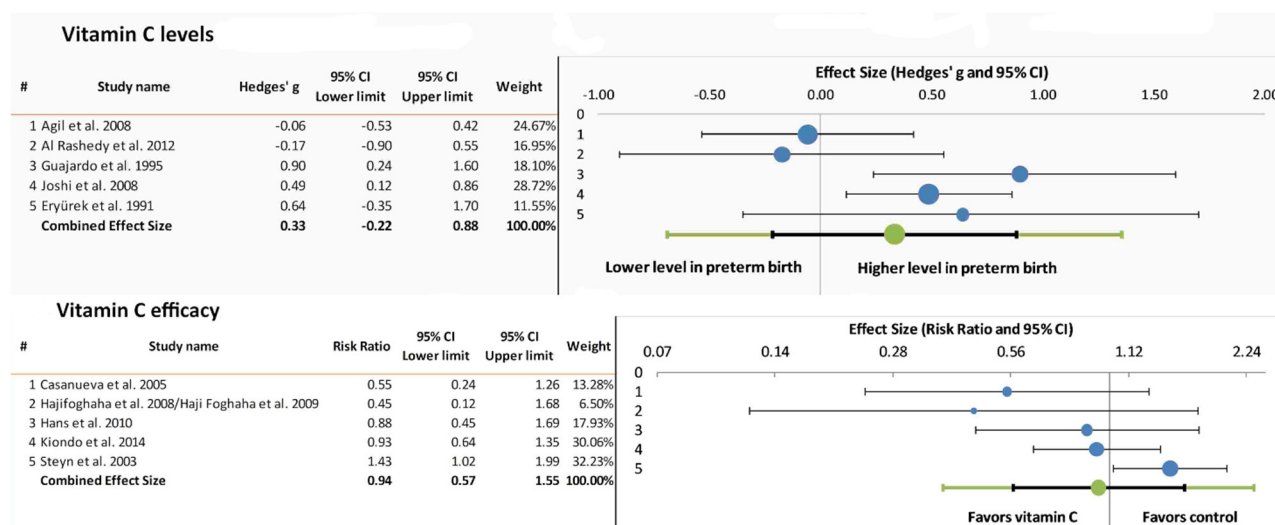
**Figure 3.** Forest plots showing effect sizes of differences in vitamin C levels between women with preterm birth and controls and effect sizes of efficacy of vitamin C supplementation in prevention of preterm birth

Table 1. Characteristics of included studies which evaluated vitamin C levels

Study ID (first author, year)	Country	Blood sample type, measurement method, time of taking the blood sample	Number of participants		Mean age $\pm$ SD in years; Mean gestational age $\pm$ SD in weeks		Mean $\pm$ SD of vitamin C levels		Conclusion	MINORS quality score and category
			Preterm birth	Control	Preterm birth	Control	Preterm birth	Control		
1	Spain	Plasma, HPLC, at delivery (within 30 minutes)	40	30	NR $\pm$ NR; NR $\pm$ NR	NR $\pm$ NR; NR $\pm$ NR	59.33 $\pm$ 16.32 μ mol/L	60.12 $\pm$ 9.04 μ mol/L	Comparable levels in both groups.	17/24 Moderate
2	Egypt	Serum, HPLC, NS	15	15	24.6 $\pm$ 3.2; 33.9 $\pm$ 1.6 (of neonates)	25.5 $\pm$ 3.4; 37.2 $\pm$ 1.6 (of neonates)	23.5 $\pm$ 11.2 μ mol/mL	25.4 $\pm$ 10.4 μ mol/mL	No significant difference between groups.	15/24 Moderate
3	USA	Plasma, HPLC, at delivery	15	25	29.5 $\pm$ 4.3; 31.4 $\pm$ 3.4 (of neonates)	26.2 $\pm$ 5.3; 39.6 $\pm$ 0.94 (of neonates)	1.33 $\pm$ 0.62 mg/dL	0.72 $\pm$ 0.69 mg/dL	Level was significantly higher in the preterm group than in the term group (p<0.05).	16/24 Moderate
4	India	Plasma, spectrophotometry, just after delivery	40	100	23.6 $\pm$ 3.3; 34.9 $\pm$ 1.8 (of neonates)	22.1 $\pm$ 2.9; 38.9 $\pm$ 1.0 (of neonates)	257.8 $\pm$ 54.1 μ mol/L	228.0 $\pm$ 63.2 μ mol/L	Level was significantly higher in the preterm group than in the term group (p=0.01).	18/24 Moderate
5	Turkey	Blood, spectrophotometry (ascorbate + dehydroascorbate), immediately after the delivery	7	10	NR $\pm$ NR; NR $\pm$ NR	NR $\pm$ NR; NR $\pm$ NR	6.08 $\pm$ 1.75 μ g/mL	4.91 $\pm$ 1.72 μ g/mL	No significant difference between groups.	14/24 Moderate

Abbreviations: HPLC – high-performance liquid chromatography; MINORS – methodological index for non-randomized studies;

NR – not reported; NS – not specified; p – statistical significance; SD – standard deviation.

Table 2. An overview of included studies evaluating efficacy of vitamin C supplementation in prevention of preterm birth

Study ID (first author, year)	Country	Inclusion criteria regarding gestational age and if previous history of preterm birth was required	Age of the participants in years (mean±SD, unless otherwise specified)	Vitamin C dosage, commencement/ duration of supplementation	Control, blinding	Frequency of preterm birth in vitamin C group (n/N)	Frequency of preterm birth in control group (n/N)	Study conclusions
1 Casanueva et al. 2005 (27)	Mexico	<20 weeks, no	Vitamin C: 27.5±7.4 Control: 27.4±7.7	100 mg daily, commenced after 20 weeks of gestation (duration not specified)	Placebo, double-blind	7/52	14/57	No significant difference (p=0.142).
2 Hajifoghaha et al. 2008 (17)/Haji Foghaha et al. 2009 (16)	Iran	20 weeks, no	Vitamin C: 23.88±4.62 Control: 24.00±4.56	100 mg daily, from 20 to 36 weeks of gestation	Placebo, single-blind	3/57	7/60	No significant difference (p=0.18).
3 Hans et al. 2010 (28)	Uganda	4 to 12 weeks, no	Median (range) Vitamin C: 24 (18-39) Control: 25 (18-37)	400 mg daily (two tablets of 100 mg two times a day), until delivery	No vitamin C, open-label	15/187	18/197	No significant difference (p=0.719).
4 Kiondo et al. 2014 (30)	Uganda	12-22 weeks, no	Age group (%) Vitamin C: ≤19 (19.5) 20-29 (53.0) 30-34 (17.0) ≥35 (10.5) Control: ≤19 (21.0) 20-29 (54.3) 30-34 (14.8) ≥35 (9.9)	1000 mg daily, until delivery	Placebo, triple-blind	47/415	51/418	No significant difference (p=0.7).
5 Steyn et al. 2003 (29)	South Africa	Before 26 weeks, history of previous preterm birth	Median (range) Vitamin C: 28 (18-44) Control: 28 (19-45)	500 mg daily (250 mg twice a day), until 34 weeks of gestation	Placebo, double-blind	50/100	35/100	Significantly more preterm birth in vitamin C group compared to control group (p=0.031).

Abbreviations: n – number of participants with preterm birth (outcome); N – number of randomized participants minus any participants whose outcomes were known to be missing (denominator); p – statistical significance; SD – standard deviation.

DISCUSSION

Our results confirm the conclusions of the previous meta-analyses that vitamin C is not effective in preventing preterm birth (6,13). This is also supported by our finding that vitamin C levels do not differ between women who had preterm birth and controls who had term delivery, as well as that both of our findings were robust in sensitivity analysis. On the other hand, part of the meta-analysis focusing only on PROM indicated that women with PROM, particularly those who develop it preterm, seem to have significantly lower levels of vitamin C, and that its supplementation seems to be effective in lowering the risk of PROM, particularly preterm PROM (14). Considering that PROM occurrence was associated with an increase in oxidative stress and abnormalities in the formation and structure of collagen, the potential ability of vitamin C to prevent PROM could be explained by its antioxidant effects and role in the synthesis of collagen (14,31,32). However, since only about 25% of preterm births is associated with PROM, while approximately 50% have unknown cause (3,4), it is likely that vitamin C doesn't play any role in these other causes which could explain its ineffectiveness in the prevention of preterm birth.

There is still no adequate standardization for reference ranges of blood vitamin C levels and units of measurement, which vary between laboratories and measurement methods (33). Reported mean vitamin C levels in the studies included in this systematic review and meta-analysis were generally above the level considered sufficient in both women who had preterm birth and controls who had term delivery (7–11). Two studies indicated that vitamin C levels were significantly higher in women who experienced preterm birth (7,8), with one study reporting that women who experienced preterm birth had mean vitamin C levels exceeding 250 $\mu\text{mol/L}$, which are usually regarded as high levels (7,33). It is well known that under normal circumstances, different tissue-recycling processes can absorb excess harmful radicals of vitamin C in blood (7,34). However, these radicals may accumulate inside the tissues and might not be as readily eliminated when antioxidant vitamin load surpasses the levels required to counteract endogenous oxidative stress which may cause a change from their beneficial antioxidant effect to a harmful prooxidant effect (7,35).

Also, it is worth noting that significant level of heterogeneity was observed in both meta-analyses which could be explained with regional differences (for both levels and efficacy), differences in measurement methods (for levels) and risk of bias (for efficacy). The influence of trial quality on heterogeneity was also observed in some of the previous meta-analyses (6). Clear regional disparities in vitamin C status and prevalence of deficiency were already observed between high-income and low- and middle-income countries, probably due to geographic, social, economic, and cultural factors (36,37). In addition, vitamin C can be measured in blood with diverse methods, many of which have limitations

and are prone to interference (37). Also, vitamin C is sensitive to oxidation, so appropriate handling, processing and storage of samples prior to analysis is very important for valid and precise measurement (37).

Our meta-analysis had some limitations that should be mentioned. First, the total number of included studies was relatively small. Therefore, our results should be interpreted cautiously, as analyses could have been underpowered. Second, although we initially planned to evaluate publication bias, we did not perform this analysis because the assessment methods are unreliable when less than ten studies are included in the meta-analysis (38). Third, significant between-study heterogeneity was observed. Although we evaluated some of the factors that could be potential sources of heterogeneity, some of them were not reported in all included studies and we also weren't able to evaluate the influence of some important factors like dietary vitamin C intake and gestational age, because these data were either not provided at all or were provided but inconsistently and only in the minority of the studies. Finally, we were not able to retrieve the full text of some reports to assess if they fulfil our criteria for inclusion, and some of the contacted authors did not reply to our request for data and clarifications, which also could have affected our results.

CONCLUSIONS

In conclusion, our results suggest that there are no significant differences in vitamin C levels between women with preterm and term birth, as well as that vitamin C supplementation doesn't influence the risk of preterm birth.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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